

PRE- CLINICAL MODELING AND SIMULATION OF RADIOFREQUENCY ABLATION IN HUMAN LUNG TUMOR

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ABSTRACT

Radio-frequency ablation (RFA) is a hyperthermia medical treatment modality, used to destroy the unwanted tissues in the human body. In this article, pre-clinical computational model has been demonstrated for attaining risk free RFA of lung tumor. The objective of this study is, to investigate the effect of variable voltages on tissues, temperature distribution and voltage requirement for radiofrequency ablation in human lung tumor by simulation model, in order to find the effect of this technology, in realistic clinical treatment. A three-dimensional right human lung and tumor has been modelled from, 2D medical image data of lung tumor patient for performing temperature-controlled RFA. This study considers the effect of using single Trocar probes in the Radiofrequency Ablation, in the lung tumour RFA and the physics behind Radiofrequency (RF) heating is discussed, to establish hyperthermia treatment planning protocols for deep seated tumours inside complex lung anatomy. The whole process is done on COMSOL MULTIPHYSICS 5.2. The temperature distribution inside the tissue and at various points inside the tumour has been predicted, by integrating two different modules of COMSOL MULTIPHYSICS (the electric currents module and the bio-heat transfer module). The results show that, the effective tumor ablation essentially depends upon, exposure time and on voltage range. The study further evaluates the range of input voltage requirement, for attaining safe ablation of tumor tissue without damaging healthy tissue during temperature controlled RFA of lung tumor. The results from the current study may be useful for the clinical practitioners, by providing them guidelines and it could make the RFA more effective and reliable.

KEYWORDS: Radiofrequency, Hyperthermia, Ablation, Trocar & Lung Tumor

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INTRODUCTION

Cancer, is a dangerous disease caused by uncontrolled growth of unwanted tissue cells in any part of the human body. This disease is increasing all around the world. If the unwanted tissue cell growth will not be controlled, then this will lead for several more deaths. There are approximately 100 type of cancers, all around the world. These different cancers are classified according to the type of cell which initiate, the cancer. According to the survey of World Health Organization and GLOBOCAN in 2012, there were approximately 14.178 million new cancer cases, arised in the world. About 8.2 million deaths were registered because of cancer, and approx. 32.63 million people were living with cancerous diseases.

[1] Worldwide, there were about 65 % (5.3 million) of cancer deaths, 48 % (15.6 million) people are living with cancer and about 57% (8.1 million) of new cancer cases were reported in the span of next 5 years.

[2]. It is believed that by 2030, there would be 21.7 million new cancer patient cases. In 2015 WHO reported, 1.69 million deaths by lung cancer, 7,88,000 deaths by liver cancer, 7,74,000 deaths by colorectal, 754,000 deaths by stomach cancer and 571,000 deaths by breast cancer.

[3]. In India by 2020, it is estimated to have 17.25 lakh of new cases of cancer patients and around 8 lakh of cancer deaths. And the cancers in the breast, lung and cervix will top the list. In 2016, Indian Council of Medical Research figures out that, there were around 14.5 lakhs of cancer cases in India. The figures reveal only 12.5 percent of patients do not go for treatment, because of treatment fear and the cost of treatment. In 2016 it was reported that, there were 1.14 lakh of new cases of lung cancer in the country.

[4] Studies reveal that, the cause for most of the diseases in India are because of Tobacco related consumable products by men, which are the main reason of lung cancer. In India the cancer disease is increasing continuously because of less availability of cancer treatment and also, because of higher costs for the surgery, for removing the cancer tumor from the human body.

[5] Less availability of treatment, inadequate, incorrect, higher cost of cancer treatment and the delayed diagnoses are the main reasons, for the less survival rate in the country.

[6,7]. The growth of unwanted cancer cells are because of number of factors like Genetic influence, Ultraviolet radiations, Carcinogenic chemicals, overexposure to estrogen, Ionizing radiation, some diets and alcohol. And the main reason for the lung cancer is smoking and use of Tobacco related eating material.

[8]. It has been noticed that, cancer is the leading cause, for most of the deaths worldwide. So many strategies have been discovered to fight cancer disease, but because of higher cost of cancer treatment and painful surgeries performed to remove cancer tumour, many patients are fearing for the treatment or, are unable to afford the treatment cost. But the treatment of cancer by Hyperthermia, is a better approach to diagnose the disease. It is also called thermal therapy. Hyperthermia, when combined with engineering, creates a new hope for the cancer patients. These treatments are adequate, less expensive and patients undergo less pain during the treatment. It comes out as promising treatment, among the other alternative methods.

Hyperthermia Treatment

Hyperthermia is a type of cancer treatment, which uses heat to destroy the unwanted cells. In this treatment the body tissues are exposed to higher temperature range, 42-50°C. This temperature can destroy the cancerous cells, without damaging the healthy tissues.

[9]. By killing the unwanted cancerous cells and structures of protein within the cell, hyperthermia may result in necrosis of tumor.

[10]. Due to the fact that, the cancerous cells are destroyed at an elevated temperature, so this treatment doesn't require any surgery.

[11] Hyperthermia is very effective, for ablation of cancerous tumor. Hyperthermia is used as a supplementary treatment to chemotherapy and Radiotherapy. It can be executed with different heating sources like, radiation applicators, external water baths and by inserting heated electrodes. By combining hyperthermia with engineering, i.e. by combining radiation therapy and chemotherapy with hyperthermia would help treat various types of cancers, including brain, lung, breast, bladder, liver, rectum, sarcoma, cervix, prostate etc. The different hyperthermia techniques used for treating cancer cells are Ultrasonic hyperthermia, microwave hyperthermia, hyperthermia perfusion, heating by catheter, by using Magnetic nano-particles and radiofrequency ablation.

[12]. This paper elaborates the pre-clinical approach to treat the cancer tumour by, radiofrequency ablation technique.

Radiofrequency Ablation Treatment

From literary reviews, it is clear that, the thermal ablation therapies are much safer and best treatment for ablation of tumor. Different therapies have their benefits for tumors, at the respective organs. The aim of therapies are, to free the patient from disease with reasonable quality life. Radiofrequency and microwave ablation are the most widely used hyperthermia therapies for the treatment of lung and breast tumor, at present.

[13-16]. The present study was on radiofrequency ablation. The term ablation means, the destruction and radiofrequency ablation (RFA) means, the heating of the tissue to cytotoxic temperature level, using radiofrequency. RFA is till date, the most studied technique. These days, this technique is widely used by clinical practitioners. Earlier studies reveal that, the RFA is not only an effective treatment for liver, but this treatment also gained interest in various other cancerous tumors such as lung, kidney, breast and prostate.

[17-20]. RFA is a faster technique than other alternative tumor treatment techniques. This technique is not complicated and the cost for the treatment is less than, other cancer treatment techniques.

In the radiofrequency ablation technique, a trocar with electrode at its tip is inserted into the lung's tumor with the help of, computer tomography image guidance technique. A high frequency AC (alternating current) ranging 450-550 kHz is placed inside the tumor, the current is passed through the electrode to the ground pad, which is placed at the back or on the thigh of the patient, for making a closed circuit and it induces frictional heat in the tissue.

[21]. The radiofrequency current is able to pass through the human body, even the human body is not a perfect conductor because of abundance of ionic fluids present in it. After the completion of the electric circuit the current starts flowing through the whole body and frictional heat is induced in the tissues, due to the agitation of free ions present in human body like, K^+ , Na^+ , Cl^- etc. Due to the frictional heat generation induced around the electrodes, the tumor tissue starts ablating. RFA is a faster technique, because within few minutes the temperature reaches $50^{\circ}C$ and within next few seconds, it reaches 60° to $70^{\circ}C$.

[22]. The temperature passed through, should be below $110^{\circ}C$ to avoid vaporization and tissue carbonization, which would result in decreased electrical conductivity in the remaining tumor tissues.

[23]. The often used electrode, in radiofrequency ablation are made of stainless steel, Ni-Ti Alloys or platinum. Some part of the electrodes remain insulated, to avoid the damage of healthy tissue. Only that part of electrode, which is inserted into the tumor tissue for destruction, would remain uninsulated. Large ground pads should be used to avoid damaging the skin in contact.

[24]. During RFA, the electromagnetic power delivered to the tissue can be controlled by different modes and these modes are namely temperature controlled mode, impedance controlled mode and power controlled mode. This study demonstrates the effects of temperature controlled mode.

The present work considered 3 dimensional lung models, to investigate the effect of temperature controlled RFA with a single electrode trocar. The objective of this study is, to investigate the effect of variable voltage, temperature distribution and voltage requirement for radiofrequency ablation in human lung tumor by simulation model, in order to find the effect of this technology in realistic clinical treatment.

METHODS AND MATERIALS

Formation of Problem

2d images (.dicom) have been taken from a patient, having cancerous tumor in his right lung, sized 13.21 mm diameter, as shown in Figure 1. As we studied in literature that, tumours having size less than 3cm can be ablated by radiofrequency ablation technique, so this case was appropriate for our study. A three dimensional lung model and a tumor inside it have been modelled by computer tomography, using (CT) scan data files (.dicom) of the lung cancer patient. The generated lung and tumour have been imported to COMSOL 5.2 multiphysics, for further simulation work

By using different tools of COMSOL, the lung and tumor were scaled to appropriate size and have been properly oriented, to coincide with the date of imported files. The complete model had been smoothed till it obtained the actual shape and volume, as shown in Figure 2, (a) & (b).

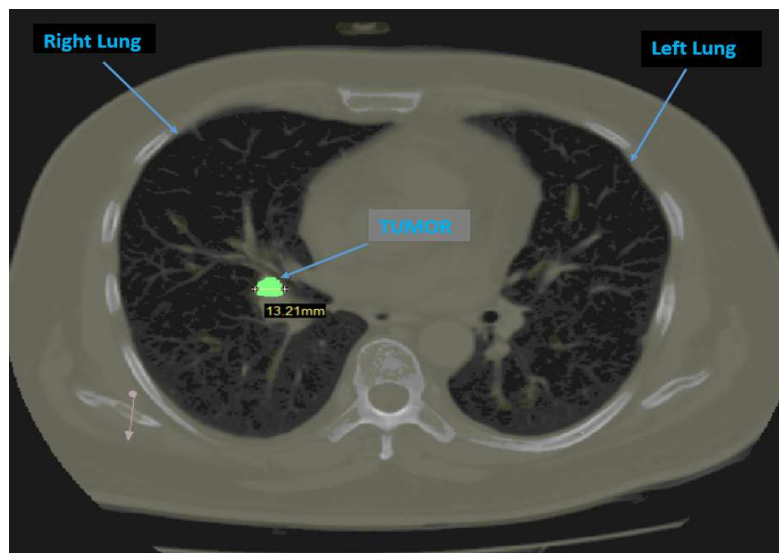


Figure 1: 2D Image from CT (Computer Tomography) of Lung and Tlung Tumor

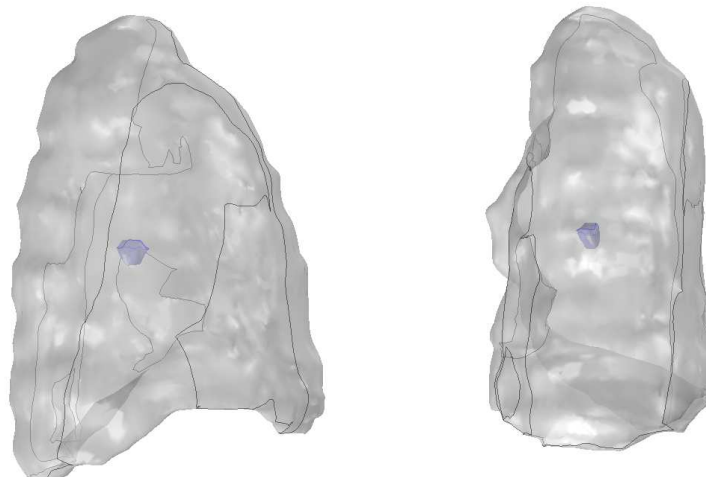


Figure 2 (a)

Figure 2 (b)

Figure 2 (A): Side View & (B): Front View of Smoothed Lung and Tumor Model in Comsol

Single trocar probe had been used, for RFA of the lung tumour. The 3 dimensional models of trocar and electrode have also been modelled in COMSOL, as shown in Figure 3. The trocar and electrode had been smoothed and processed in the same way, as it was done on lung and tumour model, for proper meshing of the entire model. The electrode has been given stainless steel properties, having good electrical conductivity and the remaining insulated portions of the trocar were given Teflon material properties.

[25, 26]. The trocar was modelled from the data available from the literature.

[27]. In this study, since the size of the tumor is small (13.21 mm), we considered using a single probe monopolar electrode, instead of using multi-probe trocar.

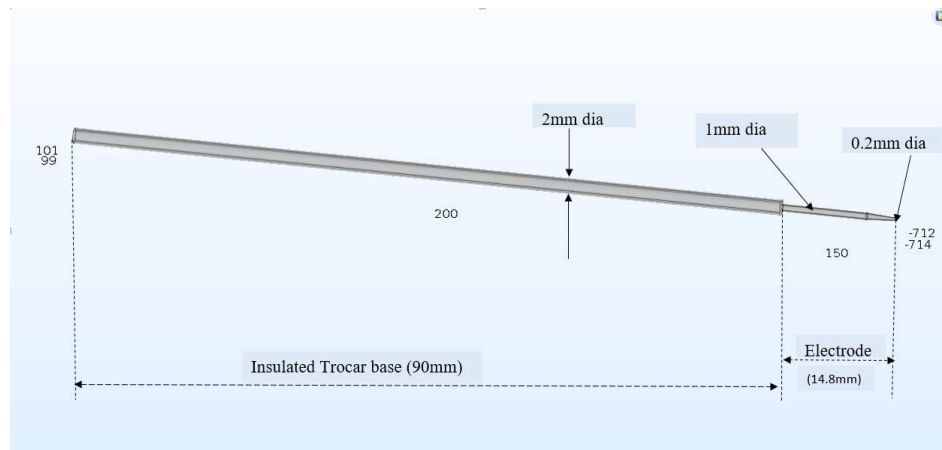


Figure 3: Trocar Used For Ablating Tumor by RFA

Mathematical Modeling in Comsol

For solving the electro-magnetic problems, quasi-statics estimation has been used because, in this range of frequency (450-550 kHz), wavelength of electromagnetic field is in multiple orders of magnitude, which is higher than the electrode active size. The generalized Laplace equation can be used, for computing the electrical field distribution within the tumour tissue, due to the applied voltage on the radiofrequency electrode. And this can be written as:

$$\nabla \cdot (\sigma \nabla V) = 0$$

(1) Here V is electrical field potential and the σ is electrical conductivity.

Furthermore, the current density (J) and the electrical field intensity (E) generation in the tissue can computed from these equations:

$$E = -\nabla V$$

$$J = \sigma E$$

(2) The tissue heating is because of local power density that is the product of electrical field intensity (E) and the current density (J) and could be written as:

$$J \cdot E = \sigma \cdot E^2$$

(3) The temperature within the lung tissue is subjected to electrical heating during the Radiofrequency ablation and has

been solved by, the Pennies equation.

$$\rho c \frac{\partial T}{\partial t} = \nabla \cdot (K \nabla T) - \rho_b c_b \omega_b (T - T_b) + Q_m + J \cdot E$$

(4) Where c , ρ and k denote heat, density and thermal conductivity respectively, in the lung tissue. c_b , ρ_b and ω_b are specific heat, density and the perfusion rate respectively, of the blood, and the Q_m is the heat generation due to the metabolic activity. Initially, this was assumed as negligible. E is the electrical field intensity, T_b is the core blood temperature (presume 37°C) and J is the current density. And finally T is the Unknown body tissue temperature.

Temperature dependent electrical conductivity has been calculated from:

$$\sigma(T) = \sigma_0 [1 + \alpha_\sigma (T - T_0)] \quad (5)$$

Here T_0 is 37°C , σ_0 is the constant electrical conductivity, at the core body temperature and in this study the temperature coefficient α_σ was assumed to be 1.5% per $^\circ\text{C}$, for tumour and the lung tissue.

[28- 29]. Thermal, Thermo-physical and electrical properties, of the lung and the tumour have been presented in the Table 1. The tissue properties have been considered at 460 kHz. For frequency below 1MHz, the dielectric losses are negligible.

[30] And these are being caused by, the rotation of atoms and molecules in the electric field.

Table 1: Electrical and Thermo-Physical Properties of Lung Tissue, Tumor Tissue, Electrode and Insulating Trocar used in RFA Modelling at 460 Khz

Properties	Electrical Properties	Thermo-Physical Properties				
Material	Σ , S/m	C, J/kg.K	K, W/m.K	ρ , kg/m ³	E_a (J/mol)	A (S ⁻¹)
Lung	0.122	3886	0.39	394	1.71×10^6	1.67×10^{280}
Electrode	10^9	840	18	6450	--	--
Tumor	0.5	3886	0.39	394	1.71×10^6	1.67×10^{280}
Trocar	10^{-5}	1045	0.026	70	--	--

INITIAL AND BOUNDARY CONDITIONS

Before the onset of Radiofrequency energy, the initial voltage of the whole domain has been considered to be zero. The single tine electrode has been set to voltage V . The trocar potential and the electrode potential have been set to a constant source potential V . Initially for the outer grounded periphery of the lung domain, electrical voltage boundary condition has been set to zero. The current within the electrode is full balanced because there is no effect of external radiation on the current at 460 kHz of Radiofrequency [31]. The temperature of lung tissue and the tumor tissues are assumed as the body room temperature (37°C). The initial temperature of the electrode has also been considered as the core body temperature. The constant voltage V has been applied for 10 minutes (600s). The electrical insulation conditions are applied to the portion inside and outside of the lung model and tumor. The potential of the electrode have been set up to a constant voltage from 18-32V. In this research, Bio-heat physics of heat transfer module and electric currents physics of AC/DC module of COMSOL 5.1 has been used to solve the FEM problem.

NUMERICAL SIMULATION

The temperature distribution in the tissues during the RFA of lung cancerous tumour has been obtained, by solving the electric field distribution equation (Eq. (1)) and the Pennies Heat equation (Eq. (4)). The entire equations have been solved in the finite element software COMSOL MULTIPHYSIC and we are using 5.1 versions, of the software for study. In this study, Bio-heat transfer (ht) physics of heat transfer module, and electric current (ec) physics of AC/DC module of COMSOL has been used for solving the FEM problems. The tetrahedral mesh elements have been used, for the meshing of entire domain. For the tumour and lung, finer mesh has been used. For the electrode and insulating portion of the trocar, minimum mesh element size has considered, 0.35mm and 1.1mm respectively and the maximum of 0.38mm for electrode and 1.3mm for trocar, has been used as shown in Figure 4. These mesh element sizes has been determined after a number of trial runs, by varying the number of meshes for each domains, but the properties were taken same for each run. This trail runs for meshing, has been done to get grid independent solution. All simulations has been carried out on Hp, Intel(R), Core(TM) i5-6200U CPU @ 2.30GHz, 2 cores and 8GB RAM.

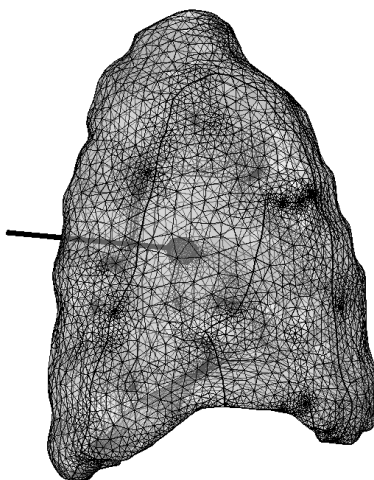


Figure 4: Meshing of Lung, TUMOR, Electrode AND Trocar

RESULTS AND DISCUSSIONS

This numerical results obtained by heating the lung tumor model with electrode, depends on tumor shape, lung and tumor tissue properties, applied voltage, trocar probe location within the tumor and heating time [32]. For validation of Radiofrequency ablation numerical technique, the results obtained from single electrode RFA in lung model cum tumor are compared with experimental results reported by Sandeep et al. [33]. The choice of cylindrical electrode has been taken from the literature review [27]. After 125 seconds the complete necrosis of the tissue is attained. The temperature necrosis relation is validated from the literature review [33]. This study result reveals the effect of target temperature on the cancerous and healthy tissue on input voltage requirement and temperature distribution during the temperature controlled RFA of lung tumor. Basically this study predicts the range of required voltage for the complete ablation of the lung tumor.

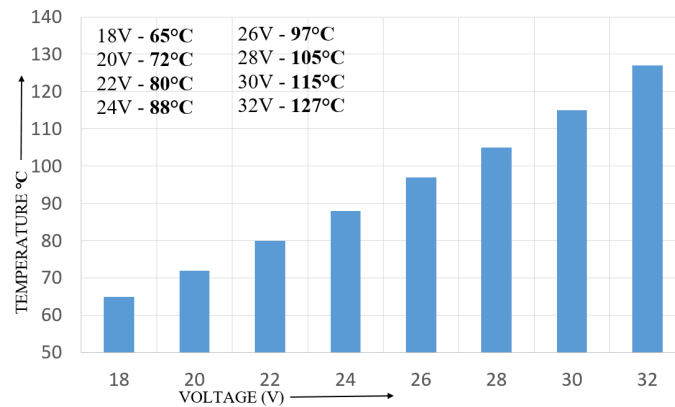


Figure 5: Temperatures at the Tip of Electrode for Different Applied Voltages

In simulation setup, the applied voltage has been varied between 15-32V. The Figure 5 depicts the different value of electrode tip temperatures on variation of applied voltage values. It also shows the input voltage requirement for attaining maximum and minimum values of temperature needed for the ablation of lung tumor. Furthermore, it has been predicted that at tip of electrode maximum temperature value increases from 65°C to 127°C as the applied voltage shifts from 18V to 32V as shown in Figure 5.

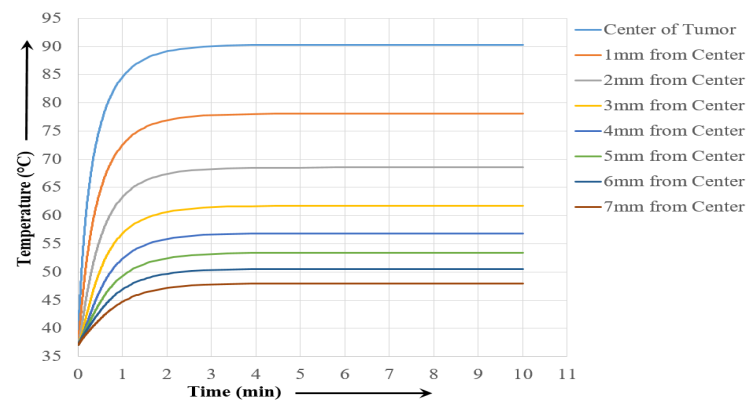


Figure 6: Variation of Temperature with Time in Tissue at Different Distances from Centre of Tumor at 24V

As seen from the Figure 6, the temperature became constant after 130sec (2min10sec). This means, the complete necrosis of tissue is done within 130sec. Figure also shows, the temperature-time variation at different points in the tissue.

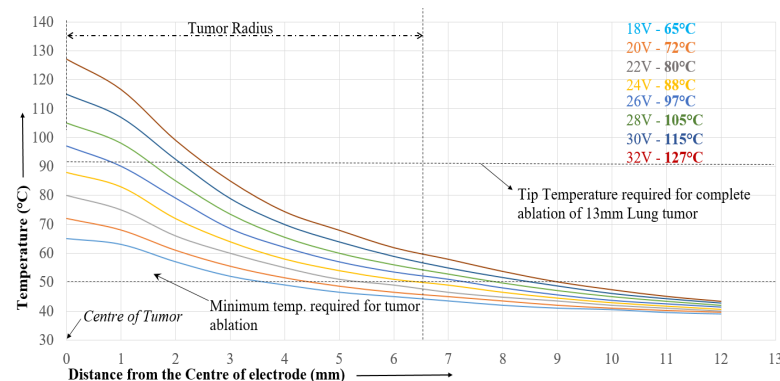
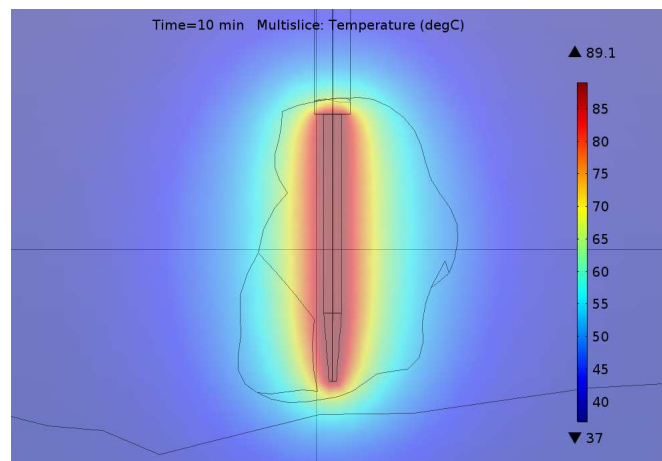


Figure 7: Temperature Distribution for Different Tip Temperatures at Varied Distance from Electrode

Because of the RF, the temperature was distributed in the entire tissue. Figure 7, represents the temperature distribution in the tumour tissue, at the tip of electrode and on points at some distance from the center of tumour, for different values of target temperature, when the voltage is applied for 10 minutes (600sec). It has been seen from the figure that, there is a significant variations in the values of temperatures at the tumor's periphery, when applying different values of target temperature. When the target temperature is set 88°C for 10 minutes, the tumour periphery temperature is noted as 50°C (minimum temperature required for tissue necrosis), during temperature controlled RFA. Hence, it is clear from figure that, the target temperature below 88°C (corresponding to 24V) is not sufficient for complete necrosis, of 13mm tumour without damaging the healthy tissue. Below this temperature, there would not be complete necrosis of the tissue.

**Figure 8: Temperature Distribution within Tumor and Healthy Tissue when Applied Voltage is 24 V for 10 Min**

As discussed earlier, the higher temperature of the tissue should be kept below or around 100°C , so as to avoid water vaporization and tissue carbonization, which leads to decrease the electrical conductivity in the remaining tumor tissue.

Moreover, it has been seen from the Figure 8 that, the maximum temperature has been noted near the surface of electrode. This figure shows the temperature distribution at all the points inside and outside the tumour.

Furthermore, it's evident from the figures that, the complete necrosis of tumor occurs when the target temperature is 88°C . For attaining tumour periphery, the temperature at least 50°C (minimum temperature for ablation) and the target temperature was below $100\text{--}105^{\circ}\text{C}$ (to resist carbonization of tissue), the range of voltage is noted from 24-28V, for a tumour of 13mm diameter. Thus, the present study reveals the significance of target temperature on the voltage requirement for Radiofrequency ablation, of lung tumour.

CONCLUSIONS

This study presents, the RF ablation treatment modelling strategies towards the risk free and effective thermal ablation of lung tumor. A simulation study has been performed on 3 dimensional realistic human anatomy model of lung

having tumour. A constant voltage has been used with single tine electrode. Multi tine electrodes can be used for ablation of larger sized tumours. An attempt has been made in this study, to find the minimum target temperature and its corresponding voltage, for the complete ablation of tumour, during temperature controlled RFA of lung tumour. The study demonstrates that, for a complete ablation of the tumour, minimum set target temperature of 88°C (corresponding to 24V) should be applied for 10 minutes, temperature below 88°C is insufficient to raise the tumour periphery temperature, 50°C is the minimum requirement for the ablation of cancerous tissue. And the maximum target temperature should be below 105°C (28V), so as to resist the coagulation of the tissue. So, it is clear from the results that, the minimum and maximum voltage required for the complete ablation of tumor should be between 24-28V. The results from the current study may be useful for the clinical practitioners, by providing them guidelines and could make the RFA more effective and reliable.

REFERENCES

1. GLOBOCAN: Country Fact Stat available at: <http://globocan.iarc.fr/factsheets/populations/factsheet.asp> estimated cancer incidence, mortality and prevalence worldwide in 2012.
2. WHO/cancer-worldhealth organisation/www.who.int/cancer/2012.
3. <http://www.who.int/mediacentre/factsheets/fs297/en>
4. <http://www.midday.com/articles/over17lakhnewcancercasesinindiaby2020icmr/17248152>
5. Swaminathan R, Rama R, Shanta V. Childhood cancers in Chennai, India, 1990–2001: incidence and survival. *Int J Cancer* 2008; 122: 2607–11.
6. Sankaranarayanan R, Swaminathan R, Brenner H, et al. Cancer survival in Africa, Asia, and Central America: a population-based study. *Lancet Oncol* 2010; 11: 165–73.
7. Sankaranarayanan R, Swaminathan R. Cancer survival in Africa, Asia, the Caribbean and Central America. IARC Sci Publication No 162. Lyon: International Agency for Research on Cancer, 2011.
8. <http://www.webindia123.com/health/disease/cancer/common/causes.htm>
9. van der Zee J. Heating the patient: a promising approach? *Annals of Oncology* 2002; 13(8):1173–1184.
10. Hildebrandt B, Wust P, Ahlers O, et al. The cellular and molecular basis of hyperthermia. *Critical Reviews in Oncology/Hematology* 2002; 43(1):33–56.
11. Andra W, d' Ambly CG, Hergt R. Temperature distribution as function of time around a small spherical heat source of local magnetic hyperthermia. *Journal of Magnetism and Magnetic Materials*. 1999. 194: 197-203.
12. Minu Sethi I, S.K. Chakarvarti, Manav Rachna International University, Faridabad, India Research and Publications, Manav Rachna International University, Faridabad, India. CODEN (USA): IJPRIF, ISSN: 0974-4304 Vol.8, No.6, pp 292-299, 2015
13. Ahmed M, Goldberg SN. Image-guided tumor ablation: Basic science. In: vanSonnenberg E, McMullen W, Solbiati L, editors. *Tumor Ablation: Principles and Practice*. New York, NY: Springer, 2005. p. 23-40.
14. Yu NC, Lu DS, Raman SS, et al. Hepatocellular carcinoma: Microwave ablation with multiple straight and loop antenna clusters—Pilot comparison with pathologic findings. *Radiology* 2006;239:269-75.
15. Kuang Christopher L. Brace, PhD, Teresa A. Diaz, MD, J. Louis Hinshaw, MD, and Fred T. Lee, Jr, MD Tissue Contraction Caused by Radiofrequency and Microwave Ablation: A Laboratory Study in Liver and Lung

16. Hines-Peralta AU, Pirani N, Clegg P, et al. Microwave ablation: Results with a 2.45-GHz applicator in ex vivo bovine and in vivo porcine liver. *Radiology* 2006;239:94-102.
17. Shah DR., Green S, Elliot A, McGahan JP, Khatri VP. Current oncologic applications of radiofrequency ablation therapies. *World Journal of Gastrointestinal Oncology* 2013;5:71-80.
18. Mirza AN, Fornage BC, Sneige N. Radiofrequency ablation of solid tumors. *Cancer J.* 2001;7:95-102.
19. Zhu JC, Yan TD, Morris DL. A systematic review of radio-frequency ablation for lung tumors. *Ann Surg Oncol* 2008;15:1765-74.
20. Fornage BD, Sneige N, Ross MI, Mirza AN, Kuerer HM, Edeiken BS, et al. Small (≤ 2 -cm) breast cancer treated with US-guided radiofrequency ablation: feasibility study. *Radiology* 2004;231:215-224.
21. Chu KF, Dupuy DE. Thermal ablation of tumours: biological mechanisms and advances in therapy. *Nature Reviews Cancer* 2014;14:199-208.
22. M.W. Miller, M.C. Ziskin, Biological consequences of hyperthermia, *Ultrasound Med. Biol.*, 15 (8), pp. 707-722 (1989).
23. D.S.K. Lu, S.S. Raman, D.J. Vodopich, M. Wang, J. Sayre and C. Lassman, Effect of vessel size and creation of hepatic radiofrequency lesions in pigs: assessment of the heat sink effect, *Am. J. Roentgenol.*, 178, pp. 47-51 (2002).
24. Steinke K, Gananadha S, King J, Zhao J, Morris DL. Dispersive pad site burns with modern radiofrequency ablation equipment. *Surg Laparosc Endosc Percutan Tech* 2003; 13(6):366-71.
25. Efunda properties of stainless steel. http://www.efunda.com/materials/alloys/alloy_home/steels_properties.cfm
26. Teflon 2014 properties <http://www.phy.davidson.edu/fachome/dmb/PY430/Friction/teflon.html>
27. Sundeep Singh, Ramjee Repaka Thermal analysis of induced damage to the healthy cell during RFA of breast tumor; *Journal of Thermal Biology* 58(2016)80-90.
28. H.H. Pennes, Analysis of tissue and arterial blood temperatures in the resting human forearm, *J. Appl. Physiol.*, 85(1), pp. 5-34 (1998).
29. Zorbas G, Samaras T. Simulation of radiofrequency ablation in real human anatomy. *International Journal of Hyperthermia* 2014;30:570-8
30. Vilhelm Ekstrand, Hans Wiksell, Inkeri Schultz, Anders Eriksson Influence of electrical and thermal properties of RF ablation of breast cancer: Is the tumour preferentially heated. *BioMedical Engineering OnLine* 2005, 4:41.
31. Ekstrand,V.,Wiksell,H.,Schultz,L.,Sandstedt,B.,Rotstein,S.,Eriksson,A.,2005.Influence of electrical and thermal properties on RF ablation of breast cancer :is the tumour preferentially heated? *Biomed. Eng. Online*4,41.
32. Z. Wang, I. Aarya, M. Gueorguieva, D. Liu, H. Luo, L. Manfredi, A. Cuschieri, Image-based 3D modeling and validation of radiofrequency interstitial tumor ablation using a tissue-mimicking breast phantom, *International Journal of Computer Assisted Radiology and Surgery*, 7(6), (2012).
33. Sundeep singh, Ramjee Repaka Temperature-controlled radiofrequency ablation of different tissues using two-compartment models. ISSN: 0265-6736 doi. 10.1080/02656736.2016.1223890.

